UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/179,002	10/26/1998	VIDYA BRAJ LOHRAY	DRF 3.0-019.	5185

70554 7590 05/28/2008

Reddy Us Therapeutics, Inc
3065 Northwoods Circle
Norcross, GA 30071

EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
05/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/179,002	LOHRAY ET AL.	
	Examiner	Art Unit	
	/Venkataraman Balasubramanian/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-10,25-27,29-31,33,34,65-68,70-72,74,75,77-80,82,83 and 85-99* is/are rejected.

7)☒ Claim(s) *24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-3,5-10,24-27,29-31,33,34,65-68,70-72,74,75,77-80,82,83 and 85-99.

DETAILED ACTION

Applicants' response, which included cancellation of claims 100-111 and amendment to claims 10 and 70, is made of record. Claims 1-3, 5-10, 24-27, 29-31, 33, 34, 65-68, 70-72, 74, 75, 77-80, 82, 83 and 85-99 are now pending. In view of applicants' response, all 112 rejections and claim objection made in the previous office action have been obviated. Upon further consideration, the Finality of the previous office action is withdrawn to apply the following new grounds of rejections.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-10, 25-27, 29-31, 33, 34, 65-68, 70-72, 74, 75, 77-80, 82, 83 and 85-99 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Recitation of "carboxylic acid or its amides or sulfonic acid…" in the R^3 definition renders claims 1, 6-10, 65, 77 and 78 renders these claims and their dependent claims in definite for more than one reason. As defined said terms "carboxylic acid or its amides or sulfonic acid…" are genus of compounds not groups. In addition the scope of amides is not clear. Also note Markush choice should be in singular. See also "thioalkyl groups" and amides of carboxylic acid recited further in these claims.

2. Recitation of "or substituted groups selected from… hydroxylalkyl, amino, acylamino, monoalkylamino, dialkylamino arylamino, aralkylamino aminoalkyl…." in the

R^3 definition renders claims 1, 6-10, 65, 77 and 78 renders these claims and their dependent claims in definite as the said “alkyl” and the “amino” are already substituted as seen above. It is not clear what is intended.

3. Claim 5 is an improper dependent claim as it fails to limit claim 1 on which it is dependent. Note R_6 definition of claim 5 is of broader scope than claim 1.

4. Claim 6 in process b recites "a Wittig reagents”. An appropriate correction is needed.

5. Recitation of “if desired” in claims 6-9 renders claims 6-9 and 65 indefinite as it is not clear when it is desirable to make salts and when it is not. Its replacement with “optionally” is suggested.

6. Claim 6 is also an improper dependent claim as it broadens the scope of R_7 in midstream of the process and thereby produces compounds which are not the same as claim 1 on which it is dependent. See in process h, R_7 is set to be same as R_6 but R_6 has a broader scope. Claim 1 does not permit such a broader scope for R_7. Also note there is a proviso in these claims to limit R_6 and R_7. Hence, it is not clear what the definition of these variables is.

7. The compound of formula IIIb shown in claim 6 has a pentavalent carbon.

8. Process (e) of claim 7 is incomplete and it is not clear what is reacted with what.

9. Recitation of “compound of formula I” in independent Claims 77 and 78 renders these claims indefinite as there is no compound of formula I shown in these claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-9 and 65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making compound of formula I with unreactive substituents as shown in examples 1-62, does not reasonably provide enablement for making compound of formula I with reactive substituents embraced in the various variable groups R^1 through $R^{7.}$ The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

In evaluating the enablement question, following factors are considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The instant claims 6-9 and 65 are drawn to various process of making compound of formula I with variable groups as embraced in R^1-R^7 including reactive groups which are also susceptible to the reaction of process or presence of which are incompatible with processes. Specification is not adequately enabled as to how to make compound of formula (I) wherein the said compound is variously substituted with reactive functional groups which are either susceptible to reaction conditions. Instant R^1, R^2, R^3,R^4, R^5, R^6, and R^7 besides other unreactive groups exemplified in examples 1-62, are permitted to

be reactive groups such as hydroxy, nitro cyano, halogen formyl, acyl, acyloxy, hydroxyalkyl, amino acylamino alkoxycarbonyl, aryloxycarbonyl, alkoxycarbonylamino, aryloxycarbonylamino, carboxylic acids amides, sulfonic acid etc. groups. All these groups are likely to participate in the process embraced in claims 6-9 and 65 or incompatible with reactants/reagents used for such processes.

For example, consider process (a) through (i) of claim 6. Process (a) requires a phosphonate of formula IIIb with a CHO group to form a carbon-carbon between the two reactants. However, there are formyl groups and acyl groups in the compound of formula IIIa which are also likely to react. Specification has no teaching or suggestion as to how to avoid such unwanted reactions. In addition, presence of free carboxylic groups and sulfonic acid groups are no compatible with the reaction. Note in the said process R^6 and R^7 set not to be hydrogen for this reason. It is also not clear how one would be able to perform the reaction in presence of hydroxyl and amino groups.

The same is true for process (b) which uses undefined Wittig reagents. It is not clear how one would be able to perform the Wittig reaction in presence of above said groups. Also it is not clear how any generic Wittig reagent would result in desired product of formula I.

Again, note process (c) requires alkylation of the nitrogen of pyrimidine (or quinazoline) with compound of formula IIId. Compound of formula IIId can also react with hydroxy, amino secondary amino, carboxylic acid group, sulfonic acid groups permitted the variable group definitions indicated above. Again specification is silent about how to perform this alkylation in presence of above said groups.

The same is true for the acylation followed by cyclization embraced in process (d). The compound of formula IIIf can also react with hydroxy, amino secondary amino, carboxylic acid group, sulfonic acid groups. Specification has no showing as to how to perform such a cyclization in presence of such reactive groups.

Similarly, process (e) which involves an aldol-like condensation of IIIf with IIIa followed by dehydration is related process a & b and has the same issues of reactive groups and incompatibility. However, there are formyl groups and acyl groups in the compound of formula IIIa which are also likely to react. Specification has no teaching or suggestion as to how to avoid such unwanted reactions. In addition, presence of free carboxylic groups and sulfonic acid groups are no compatible with the reaction. Note in the said process R^6 and R^7 set not to be hydrogen for this reason. It is also not clear how one would be able to perform the reaction in presence of hydroxyl and amino groups.

In process (f), the compound IIIh can equally react with OR^6 and or OR^7. The same is true for process (h).

In summary, the presence of various reactive functional groups stated above is incompatible with the processes a-h and would result in unwanted reaction products. Specification has no teaching or suggestion as to how to avoid such unwanted reactions.

As for process of claim 7, process (a) involves a reduction of double bond and presence of formyl, acyl and nitro groups would clearly undergo the same reduction. Specification has no teaching or suggestion as to how to avoid such unwanted

reactions. In addition, presence of hydroxy, amino, ester, carboxylic acid, sulfonic acid would also interfere in the said reduction. Again, Specification has no teaching or suggestion as to how to avoid such unwanted reactions. As for process (b), presence of halogen as substituents in the variable groups is likely to interfere with process. In addition, there can be esterification and transesterification with the alcohol IVc. In addition, R^6 as alkoxycarbonyl and aryloxycarbonyl would pose a stability problem. Specification has no teaching or suggestion as to how to get such reactive and possibly unstable IVc.

The same reasons are applicable to process (c) and process (d) which involves etherification. Presence of halogen as substituents in the variable groups is likely to interfere with process. In addition, there can be esterification and transesterification with the alcohol IIIi. Specification has no teaching or suggestion as to how to avoid such unwanted reactions.

Process (e) is incomplete. But it appears to be alkylation followed by introduction of various R^6. It appears to be alkylation of the nitrogen or carbon of pyrimidine (or quinazoline) with compound of formula IIId. Compound of formula IIId can also react with hydroxy, amino secondary amino, carboxylic acid group, sulfonic acid groups permitted the variable group definitions indicated above. Again specification is silent about how to perform this alkylation in presence of above said groups. Likewise R^6-L^3 can also react with the above said groups. Specification has no teaching or suggestion as to how to avoid such unwanted reactions.

Process (f) of claim 7 is similar to process (e) of claim 6 and has the same incompatibility issues. Process (g) involves alkylation of the nitrogen or carbon of pyrimidine (or quinazoline), IIIc with compound of formula IIId. Compound of formula IIId can also react with hydroxy, amino secondary amino, carboxylic acid group, sulfonic acid groups permitted the variable group definitions indicated above. Again specification is silent about how to perform this alkylation in presence of above said groups. Specification has no teaching or suggestion as to how to avoid such unwanted reactions. Process (h) of claim 7 is similar to process (d) of claim 6 and has the same incompatibility issues. Process (i) relates to hydrolysis of compound of formula IVf. But there are various hydrolysable groups such as esters in compound of formula I. Specification has no teaching or suggestion as to how to avoid such unwanted reactions.

Process claim 8 and process claim 65 also rely on hydrolysis of compound of formula I. But there are various hydrolysable groups such as esters in compound of formula I. Specification has no teaching or suggestion as to how to avoid such unwanted reactions.

Process claim 9 requires acyl halide or mixed anhydride to form amides with NHR^7R^8. Specification indicates several reagents for both forming acyl halide and mixed anhydride. Presence of equally reactive carboxylic acid groups and sulfonic acid groups would clearly interfere with this process. Also note presence of amino, hydroxyl etc is incompatible with the reagents.

In short, Specification offers no teachings or suggestion as to how to perform the various processes in presence of these reactive groups.

2. The predictability or lack thereof in the art:

Hence the process as applied to the above-mentioned compounds claimed by the applicant is not an art-recognized process and hence there should be adequate enabling disclosure in the specification with working example(s).

3. The amount of direction or guidance present:

Examples illustrated in the experimental section or written description offer no guidance or teachings as to how perform the processes when reactive substituents or chemically incompatible substituents are present in the starting material or reactants.

5. The presence or absence of working examples:

Although examples 1-62 show few processes, they are limited to quinazoline with no reactive functionality. There are no representative examples showing the viability of the process for plurality of reactive substituents embraced in the instant claims.

6. The breadth of the claims:

Specification has no support, as noted above, for processes of making all compounds generically embraced in the claim language would lead to desired compound of formula I with said reactive groups and there is also no valid chemical reasoning for one trained in the art to expect that all these functional groups would be inert toward the reactants and reagents embraced in the process claims

7. The quantity of experimentation needed:

The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired structure, namely compound of formula I embraced in the instant claims.

Thus, factors such as "sufficient working examples", the "level of skill in the art and predictability, etc., have been demonstrated to be sufficiently lacking in the case for the instant claims.

Claims 31,33, 34, 72, 74, 75, 83, 85, 86, 89, 91, 93, 95, 97 and 99 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating diabetes and other related disorders administering with compound of formula I along with other active ingredients, does not reasonably provide enablement for administering with compound of formula I along with other active ingredients within such a period as to act synergistically together. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, following factors are considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The instant claims 31,33, 34, 72, 74, 75, 83, 85, 86, 89, 91, 93, 95, 97 and 99 are method of treating diabetes, impaired glucose tolerance, disorders related to syndrome X, reducing plasma glucose, triglycerides, total cholesterol, LDL, VLDL and free fatty acids in the plasma by administering an effective amount of a compound of formula (I) as defined in claim 1, in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol which may be administered together or within such a period as to act synergistically together to a patient in need thereof. While use of HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol, may lower cholesterol or possibly triglycerides and thereby impart synergism with the compound of formula I , which is shown in the specification to have such actions, there is no showing both in the specification or prior art that HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol etc would equally effective treating diabetes, impaired glucose tolerance, disorders related to syndrome X, reducing plasma glucose, and insulin resistance. Hence there is unlikely to be any synergism of these agents with instant compound. Specification is not adequately enabled as to use the compound of formula (I) for synergistic action in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol. Specification offers no teachings or suggestion as to how to perform the method of treating to obtain the desired synergistic effect embraced in the instant claims.

In addition, it is not clear what is implied by "within such a period as to act synergistically together". Specification has no showing or suggestion as what is such period that imparts the synergistic effect.

2. The predictability or lack thereof in the art:

Hence, the method of use as applied to the above-mentioned compounds claimed by the applicant is not an art-recognized process and hence there should be adequate enabling disclosure in the specification with working example(s).

4. The amount of direction or guidance present: Examples illustrated in the experimental section or written description offer no guidance or teachings as to how perform the method of treating for obtaining the desired synergistic effect with respect to above indicated conditions or disorders.

5. The presence or absence of working examples:

Although examples in the specification show efficacy of the instant compounds, there is no showing of the said synergistic effect in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol There are no representative examples showing the viability of the method of use for huge genus of compounds with plurality of reactive substituents embraced in the instant claims and in combination/concomittant with HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol.

6. The breadth of the claims: Specification has no support, as noted above, for all compounds generically embraced in the claim language would lead to desired synergistic effect with compound of formula I and in combination/concomittant with

HMG CoA reductase inhibitors, fibrates, nicotinic acid, cholestyramine, colestipol or probucol and there is also no valid chemical reasoning for one trained in the art to expect such would be the case.

7. The quantity of experimentation needed:

The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the desired synergistic effect for treating diabetes, impaired glucose tolerance, disorders related to syndrome X, reducing plasma glucose, and insulin resistance.

Thus, factors such as "sufficient working examples", the "level of skill in the art and predictability, etc., have been demonstrated to be sufficiently lacking in the case for the instant claims.

Allowable Subject Matter

Claim 24 is objected to as being dependent upon a rejected base claim, but would be allowable, barring any finding of any prior art or interfering subject matter in a subsequent search, if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

It is again noted that the compounds of EP 903,343 include the present compounds. In the formula of the patent, X can be oxygen, A can be alkyleneoxy and W can be W-3 (a 4-oxo-3,4-dihydro-3-quinazinyl ring). See also Compound 1Q. While the

date of the European patent is subsequent to the effective filing date of the present application, any corresponding U.S. application or patent would involve interfering subject matter.

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

/Venkataraman Balasubramanian/

Primary Examiner, Art Unit 1624